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PATENT ABSTRACTS OF JAPAN

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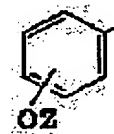
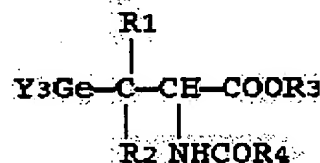
(54) ORGANOGERMANIUM COMPOUND

(57)Abstract:

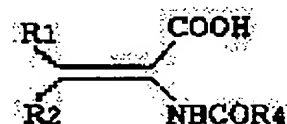
PURPOSE: To obtain a new specific organogermanium compound having an amino acid structure introduced, and a variety of pharmacological actions, particularly an action to inhibit the Maillard reaction which is regarded as a cause of food deterioration.

CONSTITUTION: The new organogermanium compound of formula I [Y is a halogen, H; R1, R3 are H, a lower alkyl; R2 is a lower alkyl, carboxylakyl, a group of formula II (Z is H, acetyl); R4 is a lower alkyl or benzyloxy], for example,

1-(1-acetamide-1-carboxymethyl)ethylgermanium sesquioxide, which has a variety of pharmacological actions, particularly an action to inhibit the Maillard reaction which is reactions of amino compounds with reducing sugars as food components and is regarded as a cause of food deterioration. The compound is obtained by addition reaction of a germanium halide of the formula: HGeY_3 to a compound of formula III in an organic solvent such as ethyl ether.



II



LEGAL STATUS

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13.02.2001

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[Date of requesting appeal against examiner's decision of rejection]

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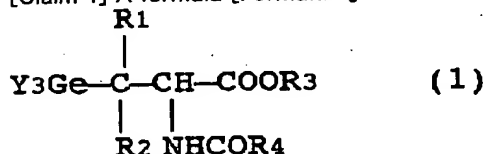
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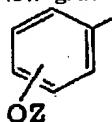
CLAIMS

[Claim(s)]

[Claim 1] A formula [Formula 1]

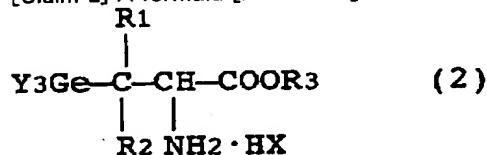


the inside of a formula, and Y — a halogen atom or a hydrogen atom — R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 2]

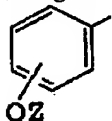


(Z expresses a hydrogen atom or an acetyl group) — R4 — a low-grade alkyl group or a benzyloxy radical — respectively — expressing — the organic germanium compound characterized by what is expressed.

[Claim 2] A formula [Formula 3]

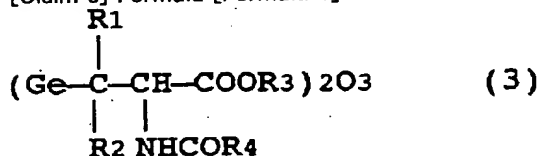


the inside of a formula, and Y — a halogen atom or a hydrogen atom — R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 4]

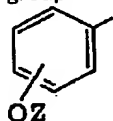


(Z expresses a hydrogen atom or an acetyl group) — X — halogen **** — respectively — expressing — the organic germanium compound characterized by what is expressed.

[Claim 3] Formula [Formula 5]

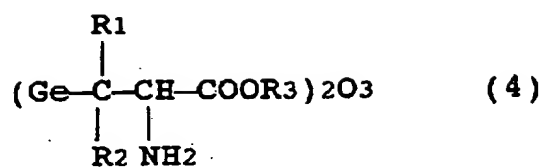


the inside of a formula, and R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 6]

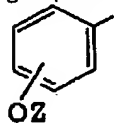


(Z expresses a hydrogen atom or an acetyl group) — R4 — a low-grade alkyl group or a benzyloxy radical — respectively — expressing — the organic germanium compound characterized by what is expressed.

[Claim 4] A formula [Formula 7]



the inside of a formula, and R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 8]



(Z expresses a hydrogen atom or an acetyl group) — respectively — expressing — the organic germanium compound characterized by what is expressed.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to an organic germanium compound.

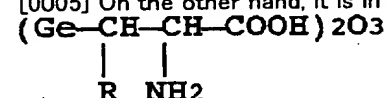
[0002]

[Description of the Prior Art] About the germanium compound which is a carbonaceous homolog, it is observed also from the field of every direction especially medicine, or pharmaceutical sciences as recent years come and the research on the organic compound and an announcement of the result come to be made actively. For example, about the carboxy ethyl germanium sesquioxide (JP,46-2498,B) which is the organic germanium compound which the propionic-acid derivative and oxygen atom of germanium combined at a rate of 2:3, it is reported that an interferon induction operation, antitumor action, etc. are shown just like [of a blood-pressure descent operation of a natural hypertension rat or not only a mitigation operation of amyloid change but a macrophage or a spontaneous killer cell] activation; and, also clinically, it is tried.

[0003] Since [2(germanium-CH₂-CH₂-COOH) O₃] it is expressed with the becoming chemical formula, if it **, and the above-mentioned carboxy ethyl germanium sesquioxide can introduce the amino group into the alpha position of carboxyl group-COOH in the above-mentioned chemical formula fundamentally, such a compound can be considered to be the so-called kind of amino acid.

[0004] It is fundamentally known for the above-mentioned amino acid well that it is the generic name of the compound expressed with the becoming chemical formula, and is what exists in all the living world where a life process is seen as a living body's indispensable constituent R-CH(NH₂) COOH. And not only in the point which amino acid combines the importance of amino acid and forms protein but in the living body, amino acid is metabolized variously and is also in the point which serves as a precursor of other important material for the living body. Therefore, if the above-mentioned amino acid structure can be introduced as that substructure to said carboxy ethyl germanium sesquioxide by which it is known that the pharmacological action which was already excellent is shown, it is fully expected that this organic germanium compound will be what shows new usefulness.

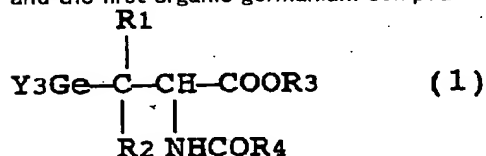
[0005] On the other hand, it is in JP,02-62885,A, [Formula 9]



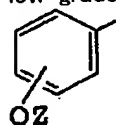
(R expresses a hydrogen atom, a low-grade alkyl group, or a phenyl group) etc. — although the organic germanium compound which has an amino group in a side chain is indicated, if organic germanium compounds other than what introduced into the official report concerned the amino acid structure currently indicated substantially are compoundable, it is expected that those compounds will be what shows still newer usefulness.

[0006]

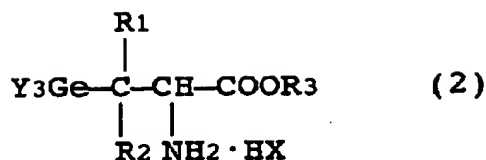
[Means for Solving the Problem] This invention was made in view of the conventional technology mentioned above, and the first organic germanium compound of this invention is a formula. [Formula 10]



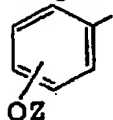
the inside of a formula, and Y — a halogen atom or a hydrogen atom — R₁ and R₃ — a hydrogen atom or a low-grade alkyl group — R₂ — a low-grade alkyl group and carboxy alkyl group — or [Formula 11]



(Z expresses a hydrogen atom or an acetyl group) — R₄ — a low-grade alkyl group or a benzyloxy radical — respectively — expressing — what is characterized by what is expressed — it is — the second organic germanium compound of this invention — a formula [Formula 12]

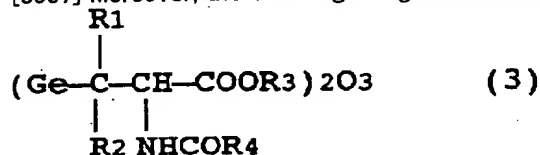


the inside of a formula, and Y — a halogen atom or a hydrogen atom — R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 13]

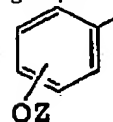


(Z expresses a hydrogen atom or an acetyl group) — X — halogen **** — respectively — expressing — it is characterized by what is expressed.

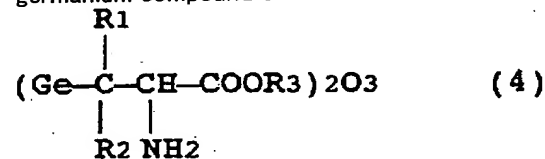
[0007] Moreover, the third organic germanium compound of this invention is a formula. [Formula 14]



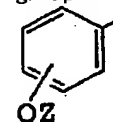
the inside of a formula, and R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 15]



(Z expresses a hydrogen atom or an acetyl group) — R4 — a low-grade alkyl group or a benzyloxy radical — respectively — expressing — what is characterized by what is expressed — it is — further — the fourth organic germanium compound of this invention — a formula [Formula 16]



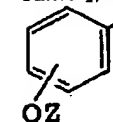
the inside of a formula, and R1 and R3 — a hydrogen atom or a low-grade alkyl group — R2 — a low-grade alkyl group and carboxy alkyl group — or [Formula 17]



(Z expresses a hydrogen atom or an acetyl group) — respectively — expressing — it is characterized by what is expressed.

[0008] This invention is explained below at details.

[0009] First, the 1st organic germanium compound of this invention While being expressed with the above-mentioned formula (1), making the propionic-acid derivative of germanium into basic structure and three substituents' Y combining with a germanium atom Two substituents R1 and R2 have combined [the amino group protected by protective groups, such as an acetyl group and a benzyloxycarbonyl radical by the alpha position in propionic-acid structure] with beta again, and the oxygen functional group of a propionic acid has become COOR3 further. the low-grade alkyl group by which Y in a formula (1) is constituted and R1 and R3 are constituted from 1 thru/about five carbon, such as a hydrogen atom or a methyl group, an ethyl group, n-propyl group, and an iso-propyl group, in a halogen atom or a hydrogen atom here — carboxy alkyl groups, such as the low-grade alkyl group as R1 with R2 [same], and a carboxymethyl radical, — or [Formula 18]



It means, respectively (Z expresses a hydrogen atom or an acetyl group).

[0010] Moreover, in the compound which is expressed with the above-mentioned formula (2) and is expressed with the above-mentioned formula (1), the second organic germanium compound of this invention is the same as the compound expressed with a formula (1), if the amino group protected by protective groups, such as an acetyl group, removes the point used as the salt of the hydrogen halide HX (X expresses a halogen atom).

[0011] On the other hand, the third organic germanium compound of this invention is expressed with a formula (3), and although this compound differs from the compound expressed with the above-mentioned formula (1) and a formula (2) with the point which the propionic-acid derivative and oxygen atom of germanium combine at a rate of 2:3, it is the same as the compound fundamentally expressed with a formula (1) except it.

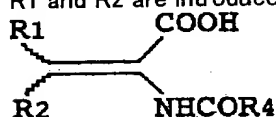
[0012] In addition, the compound expressed with the formula (1), formula (2), and formula (3) which gave [above-mentioned] explanation has very high usefulness as intermediate field at the time of compounding the fourth organic germanium compound of this invention explained below.

[0013] It ** and the final purpose compound of this invention is equivalent to that from which protective groups, such as an acetyl group which had protected the amino group in the compound which is expressed with the above-mentioned formula (4) and is expressed with the above-mentioned formula (3), were removed. namely, — an alpha position [in / this compound makes the propionic-acid derivative of germanium basic structure (however, the oxygen functional group is changed into COOR3), and / propionic-acid structure] — the amino group — moreover, while substituents R1 and R2 combine with beta, said basic structure and oxygen atom join together at a rate of 2:3.

[0014] About the above-mentioned compound (4), since it is the thing of the structure which did not exist in the former, it is expected enough that new usefulness will be shown. Then, in order to check the usefulness of the compound of above-mentioned this invention, it was the reaction of the amino compound and reducing sugar which are food constituents, and when the depressor effect of the Maillard reaction made into the cause of deterioration of food was examined, the above-mentioned compound (4) controlled the Maillard reaction effectively by low concentration.

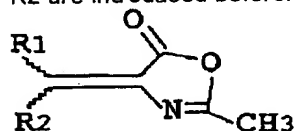
[0015] The organic germanium compound of this invention which *(ed) and gave [above-mentioned] explanation can be manufactured by the manufacture method which is explained below.

[0016] That is, for a substituent R3, the substituent Y among this invention compounds expressed with the above-mentioned formula (1) is [the thing of a hydrogen atom] the unsaturated compound into which substituents R1 and R2 are introduced beforehand with a halogen atom. [Formula 19]



What is necessary is to be alike, to receive and just to make the halogenation compound expressed with a formula HGeY3 (Y expresses a halogen atom among a formula) add. In addition, this reaction advances in organic solvents, such as ethyl ether, or inorganic solvents, such as a hydrochloric acid.

[0017] Moreover, for a substituent R3, the substituent Y among this invention compounds expressed with the above-mentioned formula (1) is [the thing of a hydrogen atom] the azlactone object into which substituents R1 and R2 are introduced beforehand with a halogen. [Formula 20]



It hydrolyzes and considers as the same unsaturated compound as the above (however, isolating is not indispensable), and even if it makes the halogenation compound expressed with a formula HGeY3 add to this unsaturated compound, it can obtain.

[0018] Furthermore, if Substituent Y can consider as the thing of a hydrogen atom among this invention compounds expressed with a formula (1) if it returns from the hydrogenation boron potassium KBH4, for example, the reactant of thionyl chloride and lower alcohol is made to act, a substituent R3 can make germanium-Y association in this invention compound expressed with the above-mentioned formula (1) the thing of a low-grade alkyl group among this invention compounds expressed with a formula (1). Of course, even if it uses together the conversion production process by these reactions, it does not interfere. The same is said of other compounds of this invention mentioned later.

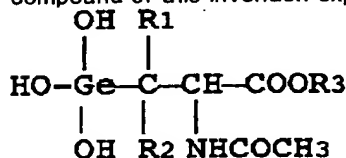
[0019] Although it can consider as the second compound of this invention expressed with the above-mentioned formula (2) if the compound expressed with the above-mentioned formula (1) is processed by hydrogen halide HY if this reaction gives the compound (however, Substituent Y removes the thing of a hydrogen atom) expressed with a formula (1) to a hydrolysis reaction that what is necessary is just to treat the compound expressed with the above-mentioned formula (1) with hydrogen halide aqueous solutions, such as a hydrochloric acid Irrespective of the class of R3, it can consider as the third compound of this invention expressed with the above-mentioned formula (3).

[0020] In addition, the thing of a hydrogen atom can be used as the third compound of this invention by which Substituent Y is expressed with a formula (3) by oxidizing this suitably among this invention compounds expressed

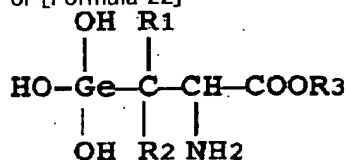
with a formula (1).

[0021] And finally it can manufacture with the fourth compound of this invention expressed with the above-mentioned formula (4) by hydrolyzing the compound (however, Substituent Y removing the thing of a hydrogen atom) expressed with the above-mentioned formula (2). In addition, the fourth compound of this invention expressed with a formula (4) can also be led from the compound expressed with a formula (1) or a formula (3).

[0022] *(ing), the spectrum data measured about the compound of this invention obtained as mentioned above is supporting well that each compound of this invention is expressed with the above-mentioned formula. In addition, the compound of this invention expressed with the above-mentioned formula (3) and (4) is at underwater, [Formula 21]



or [Formula 22]



** — structure [like] is taken.

[0023]

[Example] An example explains this invention further below at details.

[0024] After adding 6.28g (0.04 mols) of synthetic a2-acetamide-3-methyl crotonic acids of this invention compound (however, R3=H) expressed with example 1 formula (1) into 60ml concentrated hydrochloric acid and adding Tori Krol German 4.01g (0.05 mols), it agitated at the room temperature for 63 hours. When the depositing crystal was filtered, it isolated preparatively and it recrystallized [hexane / the acetone and], 9.68g (it sets at a ceremony (1) and is the compound of Y=Cl and R1=R2=R4=CH3) (71.8% of yield) of 2-acetamide-3-methyl-3-(TORIKURORU gel mill) butanoic acid was obtained.

Melting point: 150 degree-C Anal.Calcd.:C 24.94 ; H 3.59 ; N 4.15Found : C 24.93 ; H 3.58 ; N 4.07IR nu KBr/max cm-1:3330 (N-H), 1725 (C=O), 1605 (C=O), 405 1 (germanium-Cl) H-NMR (CDCl3+CD3OD) delta:1.40 (6H, s, C-(CH3) 2), 2.07 (3H, s, CO-CH3), 5.00 13 (1H, s, CH) C-NMR (Aceton-d6) delta:19.65 and 21.42 (2 (CH3)), 22.63 (N-CO-CH3), 51.29 (germanium-C), and 56.91 (CH), 171.16, 173.43 [(COO, CON changable)0025] b) Threonine 11.9g was dissolved in the aqueous solution containing 4.0g of sodium hydroxides, and ice-cooling, aqueous [containing 10.2g of acetic anhydrides and 4.0g of sodium hydroxides] was added to coincidence, and it stirred it as it was for 3 hours. N-acetyl threonine was obtained as colorless syrup almost quantitatively by adding 1Eq of dilute hydrochloric acid after reaction termination, adding ethanol to the colorless syrup obtained by distilling off a solvent by the evaporator, carrying out precipitate a ** exception, and condensing an ethanol layer.

[0026] Obtained N-acetyl threonine was dissolved in the acetic anhydride of an overlarge, and it considered as the azlactone object by stirring at a room temperature for 16 hours. Precipitate was filtered after reaction termination, by filling underwater [little by little a lot of] with filtrate, azlactone was hydrolyzed, the solvent was distilled off by the evaporator and the 2-acetamino-2-butene acid was quantitatively obtained as yellow gum-like material.

[0027] After dissolving 4.3g of obtained 2-acetamino-2-butene acids in chloroform and adding Tori Krol German 9.2g, it agitated at the room temperature for 19 hours. Distilling off of the solvent obtained quantitatively 2-acetamide-3-(TORIKURORU gel mill) butanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=R4=CH3, and R2=H) as yellow sirupy material after reaction termination.

1 H-NMR (CD3OD) delta:1.33, 1.37 (3H, d CH3 each), 2.04 (3H, s, CH3CO), 2.5-2.9 (1H, m, germanium-CM), 4.90, and 4.94 (1H, d NOC-CH each) [0028] c) In addition, other compounds expressed with a formula (1) were able to be obtained by the method indicated to Above a and b, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and a table 1.

[0029] 2-acetamide-3-(TORIKURORU gel mill) pentanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, R2=CH2CH3, and R4=CH3)

yield: — 73.7% melting point: — 163-164 degree-C Anal.Calcd.:C 24.94 ; H 3.59 ; N 4.15Found : C 24.81 ; H 3.52 ; N 4.20IR nu KBr/max cm-1:3330 (N-H), 1720 (C=O) 1640 (C=O), 430 1 (Germanium-Cl) H-NMR (Aceton-d6) Delta:1.17 (3H, T, CH3), 1.86 (1H, ddq, CH3-C-Ha) and 2.00 (1H, ddq, CH3-C-Hb), 2.08 (3H, s, CO-CH3) and 2.90 (1H, ddd, germanium-CH), 5.10 13 (1H, d, CH-CO) C-NMR (Aceton-d6) delta:13.32 (CH3), 19.99 (CH2), 22.31 (CO-CH3), 52.66 (germanium-C), and 53.32 (CH), 171.59, and 172.07 (COO, CON changable) [0030]

2-acetamide-4-methyl-3-(TORIKURORU gel mill) pentanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, R2=CH (CH3)2, and R4=CH3)

yield: — 60.1% melting point: — 119-120 degree-C Anal.Calcd.:C 27.36 ; H 4.02 ; N 3.99Found : C 27.39 ; H 4.01 ; N 3.99IR nu KBr/max cm-1:1720 (C=O), 1620 (C=O) 415 1 (Germanium-Cl) H-NMR (CDCl3, CD3OD) Delta:1.19 and 1.23 (3HX2, D, 2 (CH3)), 2.07 (3H, s, CO-CH3), 2.33 (1H, oct, 2(CH3)-CH), 2.93 (1H, dd, germanium-CH), and 5.16

(1H, d, CH-CO) [0031] 2-acetamide-3-methyl-3-(TORIKURORU gel mill) pentanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=CH3, R2=CH2CH3, and R4=CH3)

Yield: 59.4% (mixture of a diastereomer)

Melting point: 163-164 degree-C Anal.Calcld.:C 27.36 ; H 4.02 ; N 3.99 Found : C 27.05 ; H 4.19 ; N 3.88 IR nu KBr/max cm-1:3360 (N-H), 1725, 1660 (C=O), 410, 395 1 (germanium-Cl) H-NMR (CDCl3+CD3OD) delta:1.12 and 1.17 (3Hx2, tx2, germanium-C-C-CH3), 1.37, 1.42 (3Hx2, sx2, germanium-C-CH3), 1.89 (2Hx2, q, germanium-C-CH2), 2.10 (3Hx2, s, CO-CH3), and 5.18 (1Hx2, s, CH-CO) [0032] 2-(KARUBO benzyloxyamino)-3-(TORIKURORU gel mill) pentane diacid (it sets at a ceremony (1) and they are Y=Cl, R1=H, R2=CH2COOH, and the compound of R4=OCH2C6H5)

Yield: 75.1% (mixture of a diastereomer)

Melting point: 123 degree-C IR (dec.) nu KBr/max cm-1:1708(C=O) 1 H-NMR (CD3OD) delta:2.80-3.20 (3H, GeCH-CH2), 4.87 (1H, CH-N) and 5.21 (2H, CH2-ph), 7.44 13 (5H, pH) C-NMR (CD3OD) delta:31.35 and 32.64 (germanium-CH2-CH2), 54.50, 55.27 (germanium-CH2-CH), 68.33 (CH2-ph), 129.1, 129.3, and 129.7 (pH) [0033] d) After dissolving 9.2g (it sets at a ceremony (1) and is the compound of Y=Cl, R1=R4=CH3, and R2=H) of 2-acetamide-3-(TORIKURORU gel mill) butanoic acid in the potassium-hydroxide aqueous solution and being referred to as pH7, hydrogenation boron potassium 5.66g was added and it stirred for 30 minutes at the room temperature. After reaction termination, dilute hydrochloric acid was added, it was referred to as pH1, precipitate was filtered, and filtrate was extracted with ethyl-acetate ester. 4.7g (it sets at a ceremony (1) and is the compound of Y=H, R1=R4=CH3, and R2=H) of 2-acetamide-3-gel mill butanoic acid was obtained as colorless quality of a powdered material by condensing an ethyl-acetate ester layer after desiccation with sulfuric anhydride magnesium.

Yield: 71.3% (mixture of a diastereomer)

Melting point: 99-105 degree-C Anal.Calcld.:C 32.79 ; H 5.96 ; N 6.37 Found : C 32.91 ; H 6.10 ; N 6.22 IR nu KBr/max cm-1:2080 (GeH), 1710 (CO), 1610 1 (C-N) H-NMR (CD3OD) Delta:1.19 (3H, D, CH3), 1.8-2.1 (1H, m, germanium-CH), 1.97, 1.99 (each s [3H and], CH3CO), 3.58, 3.61 (3H, d GeH3 each), 4.48, and 4.57 (1H, d CH-NAc each) [0034]

[A table 1]

Y	R ₁	R ₂	R ₃	R ₄	収率
Cl	CH ₂ CH ₃	H	H	CH ₃	73.7
Cl	CH ₂ CH ₂ CH ₃	H	H	CH ₃	77.0
Cl	H	p-OH-C ₆ H ₅	H	CH ₃	87.2
Cl	CH ₃	CH ₃	CH ₂ CH ₃	CH ₃	80

[0035] 16.86g (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, and R2=CH2CH3) (0.05 mols) of synthetic a2-acetamide-3-(TORIKURORU gel mill) pentanoic acid of this invention compound (however, R3=H) expressed with example 2 formula (2) was dissolved in 40ml water, 40ml of concentrated hydrochloric acid was added, and heating reflux was carried out for 2.5 hours. the solvent was distilled off, the depositing crystal was dissolved in 100ml water, and hydrogen chloride gas was passed for about 1 hour until pyrexia stopped however. By separating the depositing crystal after cooling, the 2-amino-3-(TORIKURORU gel mill) pentanoic acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl, R1=H, and R2=CH2CH3) was considered as the white crystal, and was obtained 9.96g.

yield: — 60.1% melting point: — 180-181 degree-C(dec.) Anal.Calcld.:C 18.11 ; H 3.34 ; N 4.22 Found : C 17.92 ; H 3.31 ; N 4.02 IR nu KBr/max cm-1:1750 (C=O), 420 1 (germanium-Cl) H-NMR (CD3OD) delta:1.17 (3H, t, CH3), 1.73, 1, and 94 (1Hx2, mx2, CH3-CH2), 2.62 (1H, m, germanium-CH), 4.56 13 (1H, br, CH-N) C-NMR (CD3OD) delta:13.46 (CH3), 18.85 (CH2), and 54.12 (CH-N) [0036] b) In addition, other compounds expressed with a formula (2) were able to be obtained by the method indicated to Above a, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and a table 2.

[0037] 2-amino-4-methyl-3-(TORIKURORU gel mill) pentanoic acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl, R1=H, and R2=CH (CH3)2)

yield: — 61.0% melting point: — 165-166 degree-C(dec.) Anal.Calcld.:C 20.85 ; H 3.79 ; N 4.05 Found : C 20.80 ; H 3.90 ; N 4.35 IR nu KBr/max cm-1:1730 (C=O), 420 1 (germanium-Cl) H-NMR (CD3 OD+CDCl3) delta:1.19 and 1.29 (6H, dx2, 2 (CH3)), 2.47 (1H, oct, 2(CH3)-CH) and 3.07 (1H, dd, germanium-CH), 4.60 13 (1H, d, CH-CO) C-NMR (CD3OD) delta:21.02 and 23.71 (2 (CH3)), 27.63 (2(CH3)-CH), 50.86 (germanium-CH), 53.48 (N-CH), and 170.46 (CO) [0038] 2-amino-3-methyl-3-(TORIKURORU gel mill) butanoic acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl and R1=R2=CH3)

yield: — 88.1% melting point: — 149-150 degree-C(dec.) Anal.Calcld.:C 18.11 ; H 3.34 ; N 4.22 Found : C 18.12 ; H 3.20 ; N 4.56 IR nu KBr/max cm-1:1750 (C=O), 430, 405 1 (germanium-Cl) H-NMR (CD3 OD+CDCl3) delta:1.44 (3H, s, CH3), 1.65 (3H, s, CH3), and 4.42 (1H, s, CH-CO) [0039] 2-amino-3-methyl-3-(TORIKURORU gel mill) pentanoic acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl, R1=CH3, and R2=CH2CH3)

Yield: 61.0% (mixture of a diastereomer)

Melting point: 150 degree-C(dec.) Anal.Calcd.:C 20.85 ; H 3.79 ; N 4.05Found : C 20.55 ; H 3.98 ; N 4.47IR nu KBr/max cm-1:1765 (C=O), 420, 400 1 (germanium-Cl) H-NMR (CD3OD) delta:1.13 (3Hx2, t, germanium-C-C-CH3), 1.33, 1.57 (3Hx2, sx2, germanium-C-CH3), 1.67-2.57 (2Hx2, m, germanium-C-CH2), 4.42, and 4.52 (1Hx2, sx2, CH-CO) [0040] 2-amino-3-(TORIKURORU gel mill) pentane diacid hydrobromate (it sets at a ceremony (2) and is the compound of X=Br, Y=Cl, R1=H, and R2=CH2COOH)

Melting point: 153-degree-C(dec.) IR nu KBr/max cm-1:1723 1 (C=O) H-NMR (CD3OD) delta:2.80-3.10 (3H, germanium-CH-CH2), 4.68, and 4.78 (1H, CH-N) [0041]

[A table 2]

X	Y	R ₁	R ₂	R ₃	収率
Cl	Cl	CH ₂ CH ₃	H	H	60.1
Cl	Cl	CH ₂ CH ₂ CH ₃	H	H	69.7
Cl	Cl	H	p-OH-C ₆ H ₅	H	63.5
Cl	Cl	CH ₃	CH ₃	CH ₂ CH ₃	66.3

[0042] Synthetic a2-acetamide-4-methyl-3-(TORIKURORU gel mill) pentanoic acid of this invention compound (however, R3=CH2CH3) expressed with example 3 formula (3) (setting at a ceremony (1)) 10.53g (0.03 mols) of compounds of Y=Cl, R1=H, R2=CH (CH3)2, R3=H, and R4=CH3 was dissolved in 50ml ethanol, thionyl chloride 3.93g (0.033 mols) was added, and heating reflux was carried out for 1 hour. Since a crystal and the mixture of oily matter were obtained when the solvent was distilled off, when the ether washed this, insoluble matter was filtered and concentration hardening by drying of the filtrate was carried out, a crystal and the mixture of oily matter were obtained. This is dissolved in 300ml water and it stirs for 3 hours, and insoluble matter is filtered, a dechlorination is carried out to anion exchange resin (IRA-45, AcOH) through filtrate, and concentration hardening by drying of the filtrate is carried out, 4.02g (it sets at a ceremony (3) and is the compound of R1=H, R2=CH (CH3)2, and R4=CH3) of 1-(1-acetamide-1-ethoxy carbonylmethyl)-2-methylpropyl germanium sesquioxide was obtained as powder of fine yellow.

yield: — 56.5% melting point: — 160 degree-C(dec.) Anal.Calcd.:C 40.46 ; H 6.11 ; N 4.72Found : C 40.18 ; H 5.93 ; N 4.51IR nu KBr/max cm-1:1735 and 1660 (C=O), 875 1 (germanium-O) H-NMR (D2O) delta:1.05 (6H, m, 2 (CH3)), 1.28 (3H, t, O-C-CH3) and 2.06 (3H, s, CO-CH3), 2.07 (1H, m, 2(CH3)-CH), 2.11 (1H, m, germanium-CH), 4.23 (2H, m, O-CH2), and 4.97 (1H, d, CH-CO) [0043] b) In addition, other compounds expressed with a formula (3) were able to be obtained by the method indicated to Above a, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and a table 3.

[0044] 2-acetamide-2-(ethoxycarbonyl)-1 and 1-dimethyl-ethyl germanium sesquioxide (it sets at a ceremony (3) and is the compound of R1=R2=R4=CH3)

yield: — 59.3% melting point: — 170 degree-C(dec.) Anal.Calcd.:C 38.22 ; H 5.70 ; N 4.95Found : C 37.99 ; H 5.61 ; N 4.79IR nu KBr/max cm-1:1735 and 1660 (C=O), 860 1 (germanium-O) H-NMR (D2O) delta:1.22 and 1.25 (3Hx2, sx2, germanium-C -(CH3) 2), 1.30 (3H, t, CH2-CH3), 2.11 (3H, s, CO-CH3), 4.27 (2H, br, CH2), and 4.80 (1H, s, CO-CH) [0045] 1-(1-acetamide-1-ethoxy carbonylmethyl)-1-methylpropyl germanium sesquioxide (it sets at a ceremony (3) and is the compound of R1=R4=CH3 and R2=CH2CH3)

Yield: 32.2% (mixture of a diastereomer)

Melting point: 175 degree-C(dec.) Anal.Calcd.:C40.46 ; H 6.11 ; N 4.72Found : C40.21 ; H 5.92 ; N 4.55IR nu KBr/max cm-1:1730 and 1660 (C=O), 860 1 (germanium-O) H-NMR (CH3OD) : [1.08 (3Hx2, br, germanium-C-C-CH3),] 1.28 (6Hx2, br, germanium-C-CH3, O-C-CH3), 1.73 (2Hx2, br, germanium-C-CH2), 2.04 (3Hx2, br, CO-CH3), 4.19 (2Hx2, br, O-CH2), 4.86 [(1Hx2, br, CO-CH)0046]

[A table 3]

R ₁	R ₂	R ₃	R ₄	収率
CH ₂ CH ₃	H	CH ₂ CH ₃	CH ₃	57.0
CH ₂ CH ₂ CH ₃	H	CH ₂ CH ₃	CH ₃	61.3
H	CH ₂ COOH	CH ₂ CH ₃	CH ₃	58.2 ¹
H	p-OH-C ₆ H ₅	CH ₂ CH ₃	CH ₃	60.9

[0047] The synthetic a2-acetamide-3-gel mill butanoic acid (it sets at a ceremony (1) and is the compound of Y=H, R1=H, and R2=R4=CH3) of this invention compound (however, R3=H) expressed with example 4 formula (3) was dissolved in the mixed solvent of a methanol and dichloromethane, 3.94g of meta-KURORU perbenzoic acids was added, and it stirred for 30 minutes at the room temperature. 1.0g (it sets at a ceremony (3) and is the compound of R1=H and R2=R4=CH3) of 1-(1-acetamide-1-carboxymethyl) ethyl germanium sesquioxide was obtained as colorless powder by separating the precipitate which deposited after reaction termination and washing with the ether.

Yield: 60.1% (mixture of a diastereomer)

Melting point: 257 degree-C(dec.) Anal.Calcd.:C 38.22 ; H 5.70 ; N 4.95Found : C 38.13 ; H 5.52 ; N 4.01IR nu KBr/max cm-1:3700-2900 (NH, OH), 1720, 1650 (C=O), 880, 820 1 (germanium-O) H-NMR (D2O) delta: Diastereomer a 1.15

(3H, d, CH₃), 2.07 (3H, s, CH₃-CO) and 2.26 (1H, dq, germanium-CH), 4.82 Diastereomer b (1H, d, N-CH) 1.26 (3H, d, CH₃), 2.06 (3H, s, CH₃-CO), 2.22 (1H, dq, germanium-CH), and 4.44 (1H, d, N-CH) [0048] b) After having dissolved 1.88g (it sets at a ceremony (1) and is the compound of Y=Cl, R₁=H, R₂= PARAASETOKISHI phenyl, R₃=H, and R₄=CH₃) of 2-acetamide-3-(PARAASETOKISHI phenyl)-3-TORIKURORU gel mill propanoic acid in water, adding 1.78g of sodium hydrogencarbonates and stirring at a room temperature for 20 hours, 4.4ml of 1-N sodium-hydroxide aqueous solutions was added, and it stirred for further 2 hours. After reaction termination, dilute hydrochloric acid was added, it was referred to as pH7, and the methanol was added and filtered. Filtrate was condensed, actuation of separating the precipitate which added the methanol to residue and deposited was performed twice, and 0.82g yellow powder was obtained. It is 2 by dissolving this in distilled water and condensing a water layer after stirring cation-exchange-resin Amberlite IR120B (trade name) [H+ mold] and overnight. - 700mg (it sets at a ceremony (3) and they are R₁=H, R₂= PARAHAIDOROKISHI phenyl, and the compound of R₄=CH₃) of acetamide-2-carboxy-1-PARAHAIDOROKISHIFENIRUECHIRU germanium sesquioxide was obtained as powder of fine yellow.

Yield: 58.9% (mixture of a diastereomer)

Melting point: 300 degree-C(dec.) Anal.Calcd.:C 38.22 ; H 5.70 ; N 4.95 Found : C 38.00 ; H 5.51 ; N 4.72 IR nu KBr/max cm-1:3600-2500 (NH, OH), 1710, 1640 (C=O), 875, 840 1 (germanium-O) 1 H-NMR (D₂O) delta:1.87 (3H, s, CH₃-CO), 3.55 (1H, d, germanium-CH), 4.98 (1H, d, N-CH), 6.87 (ortho position of 2H, d, and OH), and 7.04 (meta position of 2H, d, and OH) [0049] c) 1-(1-acetamide-1-ethoxy carbonylmethyl)-2-methylpropyl germanium sesquioxide (it sets at ceremony (3) and is compound of R₁=H, R₂=CH (CH₃)₂, R₃=CH₃CH₂, and R₄=CH₃) 2.97g (0.005 mols) was suspended in 80ml water, 0.44g (0.011 mols) of sodium hydroxides was added, and it stirred for 17 hours. After filtering and carrying out desodium to cation-exchange-resin Amberlite IR120B (trade name) [H+ mold] through filtrate after reaction termination, concentration hardening by drying of the filtrate is carried out, 1.36g (it sets at a ceremony (3) and is the compound of R₁=H, R₂=CH (CH₃)₂, and R₄=CH₃) of 1-(1-acetamide-1-carboxymethyl)-2-methylpropyl germanium sesquioxide was obtained as powder of fine yellow. yield: — 50.6% melting point: — 207 degree-C(dec.) Anal.Calcd.:C35.75 ; H5.25 ; N5.21 Found : C35.56 ; H5.06 ; N5.20 IR nu KBr/max cm-1:1740 and 1665 (C=O), 875(germanium-O) 1 H-NMR (D₂O+NaOD) delta:1.06 and 1.08 (6H, d, 2 (CH₃)), 2.06 (3H, s, CO-CH₃), 1.83-2.33 (2H, m, CH-CH), and 4.56 (1H, d, CO-CH) [0050] d) In addition, other compounds expressed with a formula (3) were able to be obtained by the method indicated to Above a and b or c, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and a table 4.

[0051] The 2-acetamide-2-carboxy -1, 1-JIMECHIRUECHIRU germanium sesquioxide (it sets at a ceremony (3) and is the compound of R₁=R₂=CH₃ and R₄=CH₃)

yield: — 82.5% melting point: — 210 degree-C(dec.) Anal.Calcd.:C33.00 ; H 4.75 ; N5.50 Found : C32.71 ; H 4.61 ; N 5.27 IR nu KBr/max cm-1:1720 and 1650 (C=O), 880(germanium-O) 1 H-NMR (D₂O) delta:1.08 (3H, s, CH₃), 1.17 (3H, s, CH₃) 2.11 (3H, s, CO-CH₃), 4.62 13 (1H, s, CO-CH) C-NMR (D₂O, NaOD) delta:22.64 and 23.71 (2 (CH₃)), 24.98 (CO-CH₃), 38.54 (germanium-C), and 64.28 (CH), 176.68, and 180.06 (COO, CON changable) [0052]

1-(1-acetamide-1-carboxymethyl)-1-methylpropyl germanium sesquioxide (it sets at a ceremony (3) and is the compound of R₁=CH₃, R₂=CH₂CH₃, and R₄=CH₃)

Yield: 71.7% (mixture of a diastereomer)

Melting point: 184 degree-C(dec.) Anal.Calcd.:C35.75 ; H5.25 ; N5.21 Found : C35.63 ; H5.19 ; N 5.19 IR nu KBr/max cm-1:1720 and 1660 (C=O), 870(germanium-O) 1 H-NMR (D₂O+NaOD) delta : Diastereomer a 1.01 (3H, t, CH₃), 1.36 (1H, dq, CH₃-CHa) and 1.67 (1H dq, CH₃-CHb), 1.09 (3H, s, germanium-C-CH₃) and 2.10 (3H, s, CO-CH₃), 4.82 A diastereomer (1H, s, CO-CH) b0.99 (3H, t, CH₃), 1.50 (2H, dq, CH₃-CH₂) and 1.15 (3H, s, germanium-C-CH₃), 2.10 (3H, s, CO-CH₃), 4.65 13 (1H, s, CO-CH) C-NMR (D₂O, NaOD) delta: Diastereomer a 13.24 (germanium-C-CH₃), 20.73 (CH₃), 24.78 (CO-CH₃), and 30.77 (CH₂), 46.90 (germanium-C) 58.61 Diastereomer b (CH-CO) 12.96 (germanium-C-CH₃), 21.36 (CH₃), 24.83 (CO-CH₃), 27.94 (CH₂), 47.33 (germanium-C), 62.41 a (CH-CO), b 177.10, 177.13, 180.19, and 180.67 (COO, CON changable) [0053]

[A table 4]

R ₁	R ₂	R ₃	R ₄	収率
CH ₂ CH ₃	H	H	CH ₃	96.9
CH ₂ CH ₂ CH ₃	H	H	CH ₃	78.2
H	CH ₂ COOH	H	CH ₃	83.1

[0054] Synthetic a2-amino -3 of this invention compound (however, R₃=H) expressed with example 5 formula (4) -(TORIKURORU gel mill)- Pentanoic acid hydrochloride (in a formula (2)) 8.29g (0.025 mols) of compounds of X=Y=Cl, R₁=H, and R₂=CH₂CH₃ is dissolved in 100ml water. After making it stick to cation-exchange-resin Amberlite IR120B (trade name) [H+ mold] and rinsing, it is eluted with 2-N aqueous ammonia, and filtrate is hardened by drying. 1 -(1-amino-1-carboxymethyl)- 4.62g (it sets at a ceremony (4) and is the compound of R₁=H and R₂=CH₂CH₃) of propyl germanium sesquioxide was obtained as powder of fine yellow. yield: — 86.9% melting point: — 206 degree-C(dec.) Anal.Calcd.:C 28.23 ; H 4.74 ; N 6.5 Found : C 28.06 ; H 4.59 ; N

6.44IR nu KBr/max cm⁻¹:1630 (C=O), 870(germanium-O) 1 H-NMR (D2O) delta:1.09 (3H, t, CH₃), 1.51 (1H, ddq, CH₃-CHa) and 1.74 (1H, ddq, CH₃-CHb), 2.09 (1H, ddd, germanium-CH), 4.19 13 (1H, d, CO-CH) C-NMR (D2O) delta:15.67 (CH₃), 19.82 (CH₃-CH₂) 40.51 (germanium-CH), 57.70 (CH-N), and 176.20 (CO) [0055] b) Concentrated hydrochloric acid was added to 969mg (it sets at a ceremony (1) and they are Y=Cl, R₁=H, R₂= PARAASETOKISHI phenyl, and the compound of R₄=CH₃) of 2-acetamide-3-(PARAASETOKISHI phenyl)-3-TORIKURORU gel mill propanoic acid, and it stirred for two days at the room temperature. After reaction termination, underwater [a lot of] was filled with contents, and the impurity was filtered. It is 2 by dissolving the residue which condensed and obtained filtrate in distilled water, making it stick to cation-exchange-resin Amberlite IR120B (trade name) [H⁺ mold], being eluted with aqueous ammonia 5%, and condensing an eluate. - 200mg (it sets at a ceremony (4) and is the compound of R₁=H and R₂= PARAHAIDOROKISHI phenyl) of amino-2-carboxy-1-PARAHAIDOROKISHIFENIRUECHIRU germanium sesquioxide was obtained as powder of fine yellow.

Yield: 46.2% (mixture of a diastereomer)

Melting point: 300 degree-C>(dec.) Anal.Calcld.:C 28.23 ; H 4.74 ; N 6.5Found : C 28.00 ; H 4.56 ; N 6.32IR nu KBr/max cm⁻¹:3700-2200 (NH₃+), 1630 (NH₃+), 1605 (C=O), 885, 845 1 (germanium-O) H-NMR (D2O) delta:3.38 (1H, d, germanium-CH), 4.33 (1H, d, CO-CH), 6.87 (ortho position of 2H, d, and OH), and 7.14 (meta position of 2H, d, and OH) [0056] c) 1-(1-acetamide-1-carboxymethyl) ethyl germanium sesquioxide (it sets at ceremony (3) and is compound of R₁=H, R₂=CH₃, and R₄=CH₃) 200mg was dissolved in water, 0.2ml of concentrated hydrochloric acid was added further, and heating reflux was carried out for 18 hours. Reaction mixture was condensed after reaction termination, the obtained white crystal was again dissolved in water, the impurity was filtered, and it let filtrate pass to cation-exchange-resin Amberlite IR120B (trade name) [H⁺ mold]. After fully rinsing, it was eluted with aqueous ammonia 5.6%, and 126mg (it sets at a ceremony (4) and is the compound of R₁=H and R₂=CH₃) of 1-(1-amino-1-carboxymethyl) ethyl germanium sesquioxide was obtained as powder of an off-white by condensing an eluate.

yield: — 76.3% melting point: — 270 degree-C(dec.) Anal.Calcld.:C 24.18 ; H 4.06 ; N 7.05Found : C 24.00 ; H 3.88 ; N 6.91IR nu KBr/max cm⁻¹:3800-2500 (NH, OH), 1610 (C=O), 840, 790(germanium-O) 1 H-NMR (D2O) delta: 6.91IR nu KBr/max cm⁻¹:3800-2500 (NH, OH), 1610 (C=O), 840, 790(germanium-O) 1 H-NMR (D2O) delta: Diastereomer a 1.19 (3H, t, CH₃), 2.19 (1H, dq, germanium-CH) 4.19 Diastereomer b (1H d, CO-CH) 1.36 (3H, t, CH₃), 2.09 (1H, dq, germanium-CH), and 3.86 (1H d, CO-CH) [0057] d) In addition, other compounds expressed with a formula (4) were able to be obtained by the method indicated to Above a and b or c, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and a table 5.

[0058] 1-(1-amino-1-carboxymethyl)-2-methylpropyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R₁=H and R₂=CH (CH₃)₂)

yield: — 71.0% melting point: — 191 degree-C(dec.) Anal.Calcld.:C 31.78 ; H 5.33 ; N 6.18Found : C 31.48 ; H 5.09 ; N 6.10IR nu KBr/max cm⁻¹:1630 (C=O), 860 1 (germanium-O) H-NMR (D2O) delta:1.01 and 1.15 (6H, d, 2 (CH₃)), 2.17 (1H, d sept, 2(CH₃)-CH) and 2.29 (1H, dd, germanium-CH), 4.18 (1H, d, CH-CO) 13 C-NMR (D2O) delta:22.71, 25.84 (2 (CH₃)), 27.80 (2(CH₃)-CH), 46.03 (germanium-CH), 56.89 (CH-N), and 177.13 (CO) [0059]

1-(1-amino-1-carboxymethyl)-1-methyl-ethyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R₁=R₂=CH₃)

yield: — 80.0% melting point: — 190 degree-C(dec.) Anal.Calcld.:C 28.23 ; H 4.74 ; N 6.58Found : C 28.04 ; H 4.64 ; N 6.56IR nu KBr/max cm⁻¹:1640 (C=O), 850(germanium-O) 1 H-NMR (D2O) delta:1.53 (3H, s, CH₃), 1.36 (3H, s, CH₃), and 3.95 (1H, s, CH) [0060] 1-(1-amino-1-carboxymethyl)-1-methyl-propyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R₁=CH₃ and R₂=CH₂CH₃)

Yield: 84.6% (mixture of a diastereomer)

Melting point: 195 degree-C(dec.) Anal.Calcld.:C 31.78 ; H 5.33 ; N 6.18Found : C 31.53 ; H 5.44 ; N 6.11IR nu KBr/max cm⁻¹:1650 (C=O), 845 1 (germanium-O) H-NMR (D2O) delta:1.06 (3Hx2, t, germanium-C-C-CH₃), 1.17, 1.38 (3Hx2, sx2, germanium-C-CH₃), 1.30-2.27 (2Hx2, m, germanium-C-CH₂), 4.00, 4.19 (1Hx2, sx2, CO-CH) [0061] 2 - Amino-2-carboxy-1-(carboxymethyl) ethyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R₁=H and R₂=CH₂COOH)

Yield: 74.21% (mixture of a diastereomer)

Melting point: 345-degree-C(dec.) IR nu KBr/max cm⁻¹:1663 1 (C=O) H-NMR (D2O) delta:2.33-2.85 (3H, germanium-CH-CH₃), 4.10 13 (1H, CH-N) C-NMR (D2O, dioxane) delta:31.22 and 31.44 (germanium-CH₂-CH₂), 34.29, 34.56 (ge-CH), 52.16, 57.19 (CH-N), 174.2, and 179.7 (C=O) [0062]

[A table 5]

R ₁	R ₂	R ₃	収率
CH ₂ CH ₃	H	H	86.9
CH ₂ CH ₂ CH ₃	H	H	80.5
H	CH ₃	CH ₂ CH ₃	81.3
CH ₃	CH ₃	CH ₂ CH ₃	84.2

[0063]

[Reference experiment] Preparation undiluted solution N alpha-t-Boc-L-Lysine (50mM) of the inhibition effect 1. sample solution of a Maillard reaction with this invention compound and a glucose (1M) were dissolved in 240ml of 50ml phosphate buffers, and it considered as the undiluted solution.

It dissolved in 30ml of 50ml phosphate buffers at 30ml of control liquid undiluted solutions, and considered as control liquid.

an organic germanium compound liquid organic germanium compound — respectively — 20 — mM(s) were taken, it dissolved in the phosphate buffer of 50mM, and was referred to as 50ml, and 30ml of them was mixed with 30ml of undiluted solutions, and it considered as the organic germanium compound liquid of 10mM.

[0064] 2. Each above-mentioned sample solution was mixed as a result of the trial of the inhibition effect, it, incubated under 40-degree C shaking conditions, the sample was extracted from each on 4, 8, and the 11th, and the absorbance in 297nm (absorption maximum) was measured. A result is shown in the following table 6.

[A table 6]

化合物			吸光度(297nm)		
R ₁	R ₂	R ₃	4日目	8日目	11日目
H	CH ₂ CH ₃	H	0.37	0.54	1.35
H	p-OH-C ₆ H ₅	H	0.34	0.53	1.31
H	CH ₃	H	0.39	0.55	1.26
H	CH(CH ₃) ₂	H	0.33	0.55	1.30
CH ₃	CH ₃	H	0.33	0.51	1.25
CH ₃	CH ₂ CH ₃	H	0.32	0.52	1.21
H	CH ₂ COOH	H	0.31	0.55	1.19
CH ₂ CH ₃	H	H	0.33	0.53	1.15
H	CH ₃	CH ₂ CH ₃	0.30	0.47	1.08
CH ₃	CH ₃	CH ₂ CH ₃	0.29	0.48	1.05
H	H	H	0.39	1.17	2.78
C ₆ H ₅	H	H	0.41	1.26	2.55
コントロール			0.50	1.51	3.13

[Translation done.]

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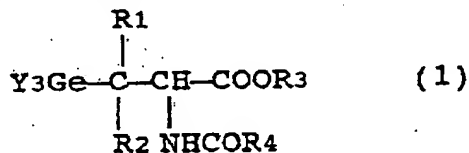
(74) 代理人 弁理士 小林 雅人 (外1名)

(54) 【発明の名称】 有機ゲルマニウム化合物

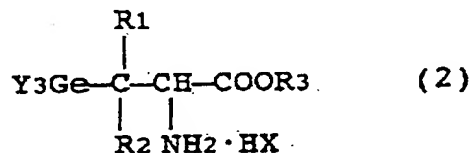
(57) 【要約】 (修正有)

【目的】 アミノ酸構造を導入した有機ゲルマニウム化合物は公知であるが、当該公知化合物と異なるアミノ酸構造を導入した有機ゲルマニウム化合物を提供する。

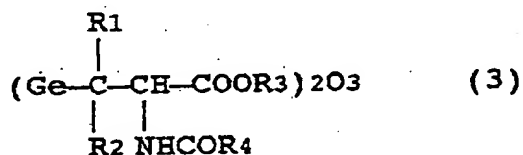
【構成】 本有機ゲルマニウム化合物は一般式1



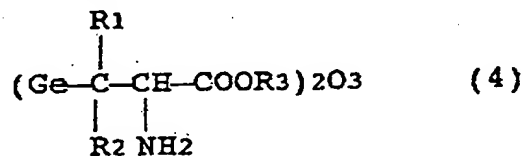
又は一般式2



又は一般式3



又は一般式4



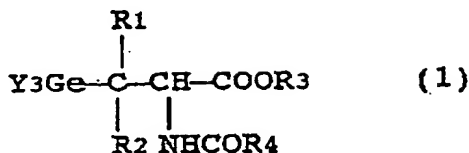
(R₁、R₂、R₃及びZは水素原子又は低級アルキル基等を、X及びYはハロゲン原子をそれぞれ表わす) で表わされる。

1

【特許請求の範囲】

【請求項1】 式

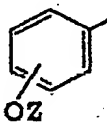
【化1】



(式中、Yはハロゲン原子又は水素原子を、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル

基、カルボキシアルキル基又は

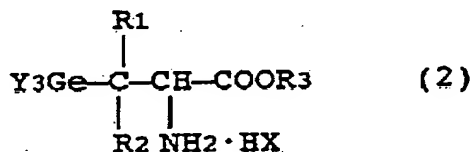
【化2】



(Zは水素原子又はアセチル基を表す)を、R₄は低級アルキル基又はベンジルオキシ基をそれぞれ表わす)で表わされることを特徴とする有機ゲルマニウム化合物。

【請求項2】 式

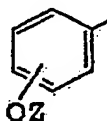
【化3】



(式中、Yはハロゲン原子又は水素原子を、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル

基、カルボキシアルキル基又は

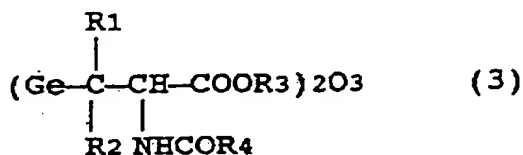
【化4】



(Zは水素原子又はアセチル基を表す)を、Xはハロゲン原子それぞれ表わす)で表わされることを特徴とする有機ゲルマニウム化合物。

【請求項3】 式

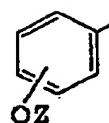
【化5】



(式中、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル基、カルボキシアルキル基又は

【化6】

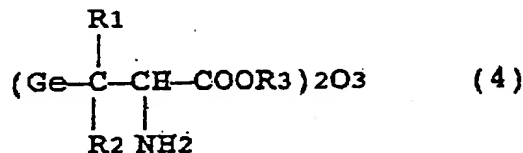
2



(Zは水素原子又はアセチル基を表す)を、R₄は低級アルキル基又はベンジルオキシ基をそれぞれ表わす)で表わされることを特徴とする有機ゲルマニウム化合物。

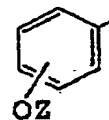
【請求項4】 式

【化7】



(式中、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル基、カルボキシアルキル基又は

【化8】



(Zは水素原子又はアセチル基を表す)をそれぞれ表わす)で表わされることを特徴とする有機ゲルマニウム化合物。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は有機ゲルマニウム化合物に関するものである。

【0002】

30 【従来の技術及び発明が解決しようとする課題】炭素の同族体であるゲルマニウムGeについては、近年になって、その有機化合物に関する研究やその結果の発表が活発に行なわれるようになるに従い、各方面、特に医学や薬学の分野からも注目されるようになってきている。例えば、ゲルマニウムのプロピオン酸誘導体と酸素原子とが2:3の割合で結合した有機ゲルマニウム化合物であるカルボキシエチルゲルマニウムセスキオキサイド(特公昭46-2498号)については、自然高血圧症ラットの血圧降下作用やアミロイド変性の軽減作用のみならず、マクロファージやNK細胞の活性化並にインターフェロン誘起作用や、抗腫瘍作用等を示すことが報告され、臨床的にも試用されている。

【0003】而して、上記カルボキシエチルゲルマニウムセスキオキサイドは、基本的に、(Ge-CH₂-CH₂-COOH)₂O₃なる化学式で表わされるものである。仮に上記化学式におけるカルボキシ基-COOHのα位にアミノ基を導入することができれば、このような化合物は、所謂アミノ酸の一種と考えることができる。

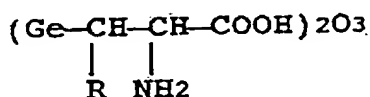
50 【0004】上記アミノ酸とは、基本的に、R-CH

3

(NH₂)COOHなる化学式で表わされる化合物の総称であって、生体の必須構成成分として、生命現象のみられる全ての生物界に存在するものであることは良く知られている。そして、アミノ酸の重要性は、アミノ酸が結合してタンパク質を形成する点のみならず、生体内においてアミノ酸は様々に代謝され、生体にとって重要な他の物質の前駆体となっている点にもあるのである。従って、すでに優れた薬理作用を示すことが知られている前記カルボキシエチルゲルマニウムセスキオキサイドに対し、その部分構造として、上記アミノ酸構造を導入できれば、この有機ゲルマニウム化合物が新たな有用性を示すものであることが十分に期待される。

【0005】一方、特開平02-62885号公報には、

【化9】

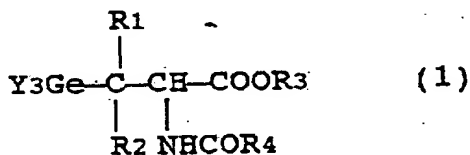


(Rは水素原子、低級アルキル基又はフェニル基を表す)等の側鎖にアミノ基を有する有機ゲルマニウム化合物が開示されているが、当該公報に実質的に開示されているアミノ酸構造を導入したもの以外の有機ゲルマニウム化合物を合成することができれば、それらの化合物が更に新たな有用性を示すものであることが期待される。

【0006】

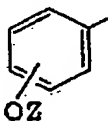
【課題を解決するための手段】本発明は上述した従来技術に鑑みてなされたもので、本発明の第一の有機ゲルマニウム化合物は、式

【化10】



(式中、Yはハロゲン原子又は水素原子を、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル基、カルボキシアルキル基又は

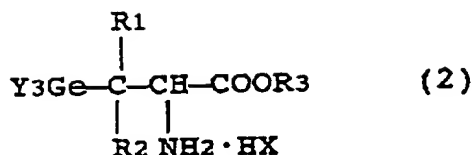
【化11】



(Zは水素原子又はアセチル基を表す)を、R₄は低級アルキル基又はベンジルオキシ基をそれぞれ表す)で表わされることを特徴とするものであり、本発明の第二の有機ゲルマニウム化合物は、式

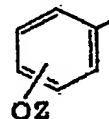
【化12】

4



(式中、Yはハロゲン原子又は水素原子を、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル基、カルボキシアルキル基又は

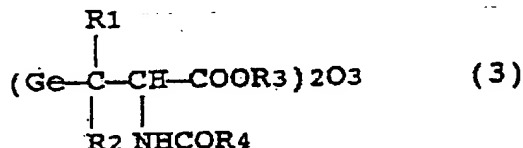
【化13】



(Zは水素原子又はアセチル基を表す)を、Xはハロゲン原子それぞれ表わす)で表わされることを特徴とするものである。

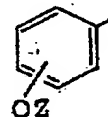
【0007】又、本発明の第三の有機ゲルマニウム化合物は、式

【化14】



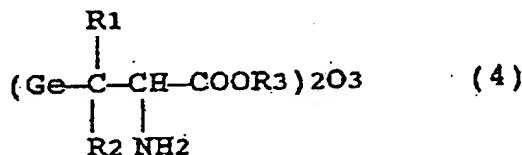
(式中、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル基、カルボキシアルキル基又は

【化15】



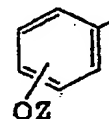
(Zは水素原子又はアセチル基を表す)を、R₄は低級アルキル基又はベンジルオキシ基をそれぞれ表わす)で表わされることを特徴とするものであり、更に、本発明の第四の有機ゲルマニウム化合物は、式

【化16】



(式中、R₁及びR₃は水素原子又は低級アルキル基を、R₂は低級アルキル基、カルボキシアルキル基又は

【化17】



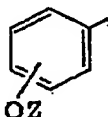
(Zは水素原子又はアセチル基を表す)をそれぞれ表わす)で表わされることを特徴とするものである。

5

【0008】以下に本発明を詳細に説明する。

【0009】先ず、本発明の第1の有機ゲルマニウム化合物は、上記式(1)で表わされるものであって、ゲルマニウムのプロピオン酸誘導体を基本構造とし、ゲルマニウム原子には置換基Yが3つ結合すると共に、プロピオン酸構造における α 位にはアセチル基やベンジルオキシカルボニル基等の保護基で保護されたアミノ基が、又、 β 位には二つの置換基 R_1 及び R_2 が結合しており、更にプロピオン酸の酸素官能基は COOR_3 となっている。ここで、式(1)中のYはハロゲン原子又は水素原子を、 R_1 及び R_3 は水素原子又はメチル基、エチル基、 n -プロピル基、 i s-o-プロピル基等の1乃至5程度の炭素で構成される低級アルキル基を、 R_2 は R_1 と同様の低級アルキル基、カルボキシメチル基等のカルボキシアルキル基又は

【化18】



(Zは水素原子又はアセチル基を表す)をそれぞれ表わしている。

【0010】又、本発明の第二の有機ゲルマニウム化合物は、上記式(2)で表わされるものであり、上記式

(1)で表わされる化合物において、アセチル基等の保護基により保護されていたアミノ基が、そのハロゲン化水素HX(Xはハロゲン原子を表わす)の塩となっている点を除いては、式(1)で表わされる化合物と同様である。

【0011】一方、本発明の第三の有機ゲルマニウム化合物は、式(3)で表わされるものであり、この化合物は、ゲルマニウムのプロピオン酸誘導体と酸素原子とが2:3の割合で結合したものである点で、上記式(1)及び式(2)で表わされる化合物と異なっているが、それ以外は基本的に式(1)で表わされる化合物と同様である。

【0012】尚、上記説明した式(1)、式(2)及び式(3)で表わされる化合物は、以下に説明する本発明の第四の有機ゲルマニウム化合物を合成する際の間接体として極めて有用性が高い。

【0013】而して、本発明の最終的な目的化合物は、上記式(4)で表わされるものであり、上記式(3)で表わされる化合物におけるアミノ基を保護していたアセチル基等の保護基が除去されたものに相当する。即ち、この化合物は、ゲルマニウムのプロピオン酸誘導体を基本構造(但し、酸素官能基は COOR_3 に変換されている)とし、プロピオン酸構造における α 位にはアミノ基が、又、 β 位には置換基 R_1 及び R_2 が結合すると共に、前記基本構造と酸素原子とが2:3の割合で結合したものである。

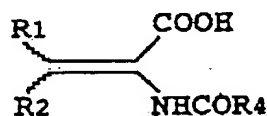
6

【0014】上記化合物(4)については、それが従来に存在しなかった構造のものであるので、新たな有用性を示すことが充分期待される。そこで、上記本発明の化合物の有用性を確認するため、食品成分であるアミノ化合物と還元糖との反応であって、食品の劣化の一因とされているメイラード反応の抑制効果を検討したところ、上記化合物(4)は、低濃度でメイラード反応を効果的に抑制したのである。

【0015】而して、上記説明した本発明の有機ゲルマニウム化合物は、次に説明するような製造方法により、製造することができる。

【0016】即ち、上記式(1)で表される本発明化合物のうち、置換基Yがハロゲン原子で置換基 R_3 が水素原子のものは、予め置換基 R_1 及び R_2 を導入してある不飽和化合物

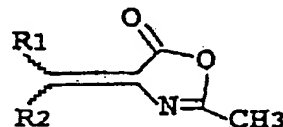
【化19】



に対し、式 HGeY_3 (式中、Yはハロゲン原子を表わす)で表わされるハロゲン化合物を付加させればよいのである。尚、この反応は、エチルエーテル等の有機溶媒中又は塩酸等の無機溶媒中で進行する。

【0017】又、上記式(1)で表される本発明化合物のうち、置換基Yがハロゲンで置換基 R_3 が水素原子のものは、予め置換基 R_1 及び R_2 を導入してあるアズラクトン体

【化20】



を加水分解して上記と同様の不飽和化合物とし(ただし、単離することは必須ではない)、この不飽和化合物に対し、式 HGeY_3 で表わされるハロゲン化合物を付加させても得ることができる。

【0018】更に、上記式(1)で表される本発明化合物における $\text{Ge}-\text{Y}$ 結合を、例えば水素化ほう素カリウム KBH_4 で還元すれば、式(1)で表される本発明化合物のうち、置換基Yが水素原子のものとすることができ、例えばチオニルクロライドと低級アルコールとの反応物と作用させれば、式(1)で表される本発明化合物のうち、置換基 R_3 が低級アルキル基のものとすることができる。もちろん、これらの反応による変換工程を併用しても差しつかえない。後述する本発明の他の化合物についても同様である。

【0019】上記式(1)で表わされる化合物をハロゲン化水素HYで処理すると、上記式(2)で表わされる

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本発明第二の化合物とすることができるが、この反応は、上記式(1)で表わされる化合物を塩酸等のハロゲン化水素水溶液により扱えばよく、又、式(1)で表わされる化合物(但し、置換基Yが水素原子のものを除く)を加水分解反応に付すと、R₃の種類にかかわらず、上記式(3)で表わされる本発明第三の化合物とすることができる。

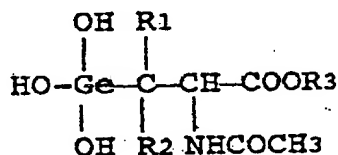
【0020】尚、式(1)で表される本発明化合物のうち、置換基Yが水素原子のものは、これを適宜に酸化することによって、式(3)で表わされる本発明第三の化合物とすることができる。

【0021】そして、上記式(2)で表わされる化合物(但し、置換基Yが水素原子のものを除く)を加水分解することにより、最終的に、上記式(4)で表わされる本発明第四の化合物と製造することができるのである。

尚、式(4)で表わされる本発明第四の化合物は、式(1)又は式(3)で表される化合物より導くこともできる。

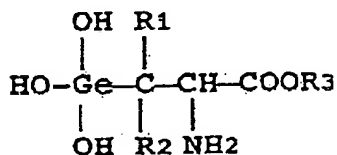
【0022】而して、以上のようにして得られた本発明の化合物について測定したスペクトルデータは、本発明の化合物がいずれも上記の式で表されることを良く支持している。尚、上記式(3)及び(4)で表される本発明の化合物は、水中では、

【化21】



又は

【化22】



のような構造をとっているものである。

【0023】

【実施例】以下に本発明を実施例により更に詳細に説明する。

【0024】実施例1

式(1)で表される本発明化合物(但しR₃=H)の合成

a) 2-アセトアミド-3-メチルクロトン酸6.28g(0.04mol)を60mlの濃塩酸中に加え、トリクロルゲルマン4.01g(0.05mol)を加えた後、室温で63時間攪拌した。析出した結晶を濾過して分取し、アセトン及びヘキサンから再結晶すると、2-アセトアミド-3-メチル-3-(トリクロルゲルミル)ブタン酸(式(1)において、Y=C1、R₁=R₂

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=R₄=CH₃の化合物)が9.68g(収率71.8%)得られた。

融点:150°C(dec.)

Anal.Calcld.:C 24.94; H 3.59; N 4.15

Found :C 24.93; H 3.58; N 4.07

IR ν KBr/max cm⁻¹: 3330 (N-H), 1725 (C=O), 1605 (C=O), 405 (Ge-Cl)

¹H-NMR (CDCl₃+CD₃OD) δ: 1.40 (6H, s, C-(CH₃)₂), 2.07 (3H, s, CO-CH₃), 5.00 (1H, s, CH)

¹³C-NMR (Aceton-d₆) δ: 19.65, 21.42 ((CH₃)₂), 22.63 (N-CO-CH₃), 51.29 (Ge-C), 56.91 (CH), 171.16, 173.43 (COO, CON changeable)

【0025】b) スレオニン11.9gを、水酸化ナトリウム4.0gを含む水溶液に溶解し、氷冷しながら、無水酢酸10.2gと水酸化ナトリウム4.0gを含む水溶液を同時に加え、そのまま3時間攪拌した。反応終了後、希塩酸を1当量加え、エバポレーターで溶媒を留去して得られた無色のシロップにエタノールを加え、沈殿を濾別し、エタノール層を濃縮することにより、ほぼ定量的にN-アセチルスレオニンを無色のシロップとして得た。

【0026】得られたN-アセチルスレオニンを大過剰の無水酢酸に溶解し、室温で16時間攪拌することにより、アズラクトン体とした。反応終了後、沈殿を濾過し、濾液を少しずつ大量の水中に注ぐことによりアズラクトンを加水分解し、エバポレーターで溶媒を留去して、2-アセトアミノ-2-ブテン酸を定量的に黄色ガム状物質として得た。

【0027】得られた2-アセトアミノ-2-ブテン酸4.3gをクロロホルムに溶解し、トリクロルゲルマン9.2gを加えた後、室温で19時間攪拌した。反応終了後、溶媒を留去すると、2-アセトアミド-3-(トリクロルゲルミル)ブタン酸(式(1)において、Y=C1、R₁=R₄=CH₃、R₂=Hの化合物)を定量的に黄色シロップ状物質として得た。

¹H-NMR (CD₃OD) δ: 1.33, 1.37 (3H, 各d, CH₃), 2.04 (3H, s, CH₃CO), 2.5~2.9 (1H, m, Ge-CH), 4.90, 4.94 (1H, 各d, NOC-CH)

【0028】c) 尚、式(1)で表される他の化合物も、上記a又はbに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表1に例示するとおりである。

【0029】2-アセトアミド-3-(トリクロルゲルミル)ペンタン酸(式(1)において、Y=C1、R₁=H、R₂=CH₂CH₃、R₄=CH₃の化合物)

収率: 73.7%

融点: 163~164°C

Anal.Calcld.: C 24.94; H 3.59; N 4.15

Found :C 24.81; H 3.52; N 4.20

IR ν KBr/max cm⁻¹: 3330 (N-H), 1720 (C=O), 164

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0 (C=O), 430 (Ge-Cl)

 $^1\text{H-NMR}$ (Aceton- d_6) δ : 1.17 (3H, t, CH_3), 1.86 (1H, ddq, $\text{CH}_3\text{-C-Ha}$), 2.00 (1H, ddq, $\text{CH}_3\text{-C-Hb}$), 2.08 (3H, s, CO-CH_3), 2.90 (1H, ddd, Ge-CH), 5.10 (1H, d, CH-CO)

 $^{13}\text{C-NMR}$ (Aceton- d_6) δ : 13.32 (CH_3), 19.99 (C-Hz), 22.31 (CO- CH_3), 52.66 (Ge-C), 53.32 (CH), 171, 59, 172.07 (COO, CON changable)

【0030】 2-アセトアミド-4-メチル-3-(トリクロルゲルミル) ペンタン酸 (式 (1) において、Y = Cl, $R_1 = \text{H}$, $R_2 = \text{CH}(\text{CH}_3)_2$, $R_4 = \text{CH}_3$ の化合物)

収率: 60.1%

融点: 119~120°C

Anal. Calcd.: C 27.36; H 4.02; N 3.99

Found: C 27.39; H 4.01; N 3.99

 IR ν KBr/max cm^{-1} : 1720 (C=O), 1620 (C=O), 415 (Ge-Cl)

 $^1\text{H-NMR}$ (CDCl_3 , CD_3OD) δ : 1.19, 1.23 (3H \times 2, d, (CH_3) $_2$), 2.07 (3H, s, CO- CH_3), 2.33 (1H, oct, (CH_3) $_2$ -CH), 2.93 (1H, dd, Ge-CH), 5.16 (1H, d, CH-CO)

【0031】 2-アセトアミド-3-メチル-3-(トリクロルゲルミル) ペンタン酸 (式 (1) において、Y = Cl, $R_1 = \text{CH}_3$, $R_2 = \text{CH}_2\text{CH}_3$, $R_4 = \text{CH}_3$ の化合物)

収率: 59.4% (ジアステレオマーの混合物)

融点: 163~164°C

Anal. Calcd.: C 27.36; H 4.02; N 3.99

Found: C 27.05; H 4.19; N 3.88

 IR ν KBr/max cm^{-1} : 3360 (N-H), 1725, 1660 (C=O), 410, 395 (Ge-Cl)

 $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ : 1.12, 1.17 (3H \times 2, t \times 2, Ge-C-C- CH_3), 1.37, 1.42 (3H \times 2, s \times 2, Ge-C- CH_3), 1.89 (2H \times 2, q, Ge-C-CH $_2$), 2.10 (3H \times 2, s, CO-C $_2$), 5.18 (1H \times 2, s, CH-CO)

*

1.0

* 【0032】 2-(カルボベンジルオキシアミノ)-3-(トリクロルゲルミル) ペンタン二酸 (式 (1) において、Y = Cl, $R_1 = \text{H}$, $R_2 = \text{CH}_2\text{COOH}$, $R_4 = \text{OCH}_2\text{C}_6\text{H}_5$ の化合物)

収率: 75.1% (ジアステレオマーの混合物)

融点: 123°C (dec.)

 IR ν KBr/max cm^{-1} : 1708 (C=O)
 $^1\text{H-NMR}$ (CD_3OD) δ : 2.80~3.20 (3H, GeCH-CH $_2$), 4.87 (1H, CH-N), 5.21 (2H, CH $_2$ -ph), 7.44 (5H, pH)

 $^{13}\text{C-NMR}$ (CD_3OD) δ : 31.35, 32.64 (Ge-CH $_2$ -CH $_2$), 54.50, 55.27 (Ge-CH $_2$ -CH), 68.33 (CH $_2$ -ph), 129.1, 129.3, 129.7 (pH)

【0033】 d) 2-アセトアミド-3-(トリクロルゲルミル) ブタン酸 (式 (1) において、Y = Cl, $R_1 = R_4 = \text{CH}_3$, $R_2 = \text{H}$ の化合物) 9.2g を水酸化カリウム水溶液に溶解し、pH 7 とした後、水素化ほう素カリウム 5.66g を加え、室温で 30 分間攪拌した。反応終了後、希塩酸を加えて pH 1 とし、沈殿を濾過し、濾液を酢酸エチルエステルで抽出した。酢酸エチルエステル層を無水硫酸マグネシウムで乾燥後、濃縮することにより、2-アセトアミド-3-ゲルミルブタン酸 (式 (1) において Y = H, $R_1 = R_4 = \text{CH}_3$, $R_2 = \text{H}$ の化合物) を無色の粉状物質として 4.7g 得た。

収率: 71.3% (ジアステレオマーの混合物)

融点: 99~105°C

Anal. Calcd.: C 32.79; H 5.96; N 6.37

Found: C 32.91; H 6.10; N 6.22

 IR ν KBr/max cm^{-1} : 2080 (GeH), 1710 (CO), 1610 (C-N)

 $^1\text{H-NMR}$ (CD_3OD) δ : 1.19, (3H, d, CH_3), 1.8~2.1 (1H, m, Ge-CH), 1.97, 1.99 (3H, 各 s, CH_3CO), 3.58, 3.61 (3H, 各 d, GeH $_3$), 4.48, 4.57 (1H, 各 d, CH-Nac)

【0034】

【表1】

Y	R_1	R_2	R_3	R_4	収率
Cl	CH_2CH_3	H	H	CH_3	73.7
Cl	$\text{CH}_2\text{CH}_2\text{CH}_3$	H	H	CH_3	77.0
Cl	H	p-OH-C $_6$ H $_5$	H	CH_3	87.2
Cl	CH_3	CH_3	CH_2CH_3	CH_3	80

【0035】 実施例2

式 (2) で表される本発明化合物 (但し $R_3 = \text{H}$) の合成

a) 2-アセトアミド-3-(トリクロルゲルミル) ペンタン酸 (式 (1) において、Y = Cl, $R_1 = \text{H}$, $R_2 = \text{CH}_2\text{CH}_3$ の化合物) 16.86g (0.05mol) を 40ml の水に溶解し、濃塩酸 40ml を加えて ※50

※2.5時間加熱還流した。溶媒を留去し、析出した結晶を 100ml の水に溶解し、塩化水素ガスを約 1 時間 (但し、発熱が停止するまで) 流した。冷却後、析出した結晶を濾取することにより、2-アミノ-3-(トリクロルゲルミル) ペンタン酸塩酸塩 (式 (2) において、X=Y=Cl, $R_1 = \text{H}$, $R_2 = \text{CH}_2\text{CH}_3$ の化合物) を白色結晶として 9.96g 得た。

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収率: 60.1%

融点: 180~181°C(dec.)

Anal.Calcd.: C 18.11; H 3.34; N 4.22

Found : C 17.92; H 3.31; N 4.02

IR ν KBr/max cm^{-1} : 1750 (C=O), 420 (Ge-Cl) $^1\text{H-NMR}$ (CD_3OD) δ : 1.17 (3H, t, CH_3), 1.73, 1.94 (1H \times 2, m \times 2, $\text{CH}_3\text{-CH}_2$), 2.62 (1H, m, Ge-CH), 4.56 (1H, br, CH-N) $^{13}\text{C-NMR}$ (CD_3OD) δ : 13.46 (CH_3), 18.85 (CH_2), 54.12 (CH-N)

【0036】b) 尚、式(2)で表される他の化合物も、上記aに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表2に例示するとおりである。

【0037】2-アミノ-4-メチル-3-(トリクロルゲルミル)ペンタン酸塩酸塩(式(2)において、X=Y=Cl, $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}(\text{CH}_3)$ の化合物)

収率: 61.0%

融点: 165~166°C(dec.)

Anal.Calcd.: C 20.85; H 3.79; N 4.05

Found : C 20.80; H 3.90; N 4.35

IR ν KBr/max cm^{-1} : 1730 (C=O), 420 (Ge-Cl) $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}+\text{CDCl}_3$) δ : 1.19, 1.29 (6H, d \times 2, (CH_3) $_2$), 2.47 (1H, oct, (CH_3) $_2\text{-CH}$), 3.07 (1H, dd, Ge-CH), 4.60 (1H, d, CH-CO) $^{13}\text{C-NMR}$ (CD_3OD) δ : 21.02, 23.71 ((CH_3) $_2$), 27.63 ((CH_3) $_2\text{-CH}$), 50.86 (Ge-CH), 53.48 (N-CH), 170.46 (CO)【0038】2-アミノ-3-メチル-3-(トリクロルゲルミル)ブタン酸塩酸塩(式(2)において、X=Y=Cl, $\text{R}_1=\text{R}_2=\text{CH}_3$ の化合物)

30 【表2】*

X	Y	R_1	R_2	R_3	収率
Cl	Cl	CH_2CH_3	H	H	60.1
Cl	Cl	$\text{CH}_2\text{CH}_2\text{CH}_3$	H	H	69.7
Cl	Cl	H	p-OH-C $_6$ H $_5$	H	63.5
Cl	Cl	CH_3	CH_3	CH_2CH_3	66.3

【0042】実施例3

式(3)で表される本発明化合物(但し $\text{R}_3=\text{CH}_2\text{CH}_3$)の合成

a) 2-アセトアミド-4-メチル-3-(トリクロルゲルミル)ペンタン酸(式(1)において、Y=Cl, $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}(\text{CH}_3)$, $\text{R}_3=\text{H}$, $\text{R}_4=\text{CH}_3$ の化合物) 10.53g (0.03mol)を50mlのエタノールに溶解し、チオニルクロライド3.93g (0.033mol)を加えて1時間加熱還流した。溶媒を留去すると結晶と油状物の混合物が得られるので、これをエーテルで洗浄し、不溶物を濾過して濾液を濃縮乾固すると、結晶と油状物の混合物が得られた。これを300mlの水に溶解して3時間攪拌し、不溶物を濾過(50

12

*収率: 88.1%

融点: 149~150°C(dec.)

Anal.Calcd.: C 18.11; H 3.34; N 4.22

Found : C 18.12; H 3.20; N 4.56

IR ν KBr/max cm^{-1} : 1750 (C=O), 430, 405 (Ge-Cl) $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}+\text{CDCl}_3$) δ : 1.44 (3H, s, CH_3), 1.65 (3H, s, CH_3), 4.42 (1H, s, CH-CO)【0039】2-アミノ-3-メチル-3-(トリクロルゲルミル)ペンタン酸塩酸塩(式(2)において、X=Y=Cl, $\text{R}_1=\text{CH}_3$, $\text{R}_2=\text{CH}_2\text{CH}_3$ の化合物)

収率: 61.0% (ジアステレオマーの混合物)

融点: 150°C(dec.)

Anal.Calcd.: C 20.85; H 3.79; N 4.05

Found : C 20.55; H 3.98; N 4.47

IR ν KBr/max cm^{-1} : 1765 (C=O), 420, 400 (Ge-Cl) $^1\text{H-NMR}$ (CD_3OD) δ : 1.13 (3H \times 2, t, Ge-C-C- CH_3), 1.33, 1.57 (3H \times 2, s \times 2, Ge-C- CH_3), 1.67~2.57 (2H \times 2, m, Ge-C- CH_2), 4.42, 4.52 (1H \times 2, s \times 2, CH-CO)【0040】2-アミノ-3-(トリクロルゲルミル)ペンタン二酸臭化水素酸塩(式(2)において、X=B, Y=Cl, $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}_2\text{COOH}$ の化合物)

融点: 153°C(dec.)

IR ν KBr/max cm^{-1} : 1723 (C=O) $^1\text{H-NMR}$ (CD_3OD) δ : 2.80~3.10 (3H, Ge-CH- CH_2), 4.68, 4.78 (1H, CH-N)

【0041】

※して濾液を陰イオン交換樹脂(IRA-45, AcOH)に通して脱塩素し、濾液を濃縮乾固することによ

り、1-(1-アセトアミド-1-エトキシカルボニルメチル)-2-メチルプロピルゲルマニウムセスキオキサイド(式(3)において、 $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}(\text{CH}_3)$, $\text{R}_3=\text{CH}_3$ の化合物)を、微黄色の粉末として4.02g得た。

収率: 56.5%

融点: 160°C(dec.)

Anal.Calcd.: C 40.46; H 6.11; N 4.72

Found : C 40.18; H 5.93; N 4.51

IR ν KBr/max cm^{-1} : 1735, 1660 (C=O), 875 (Ge-O)

13

$^1\text{H-NMR}$ (D_2O) δ : 1.05 (6H, m, $(\text{CH}_3)_2$), 1.28 (3H, t, O-C-CH_3), 2.06 (3H, s, CO-CH_3), 2.07 (1H, m, $(\text{CH}_3)_2\text{-CH}$), 2.11 (1H, m, Ge-CH), 4.23 (2H, m, O-CH_2), 4.97 (1H, d, CH-CO)

【0043】b) 尚、式(3)で表される他の化合物も、上記aに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表3に例示するとおりである。

【0044】2-アセトアミド-2-(エトキシカルボニル)-1,1-ジメチル-エチルゲルマニウムセスキオキサイド(式(3)において、 $\text{R}_1=\text{R}_2=\text{R}_4=\text{CH}_3$ の化合物)

収率: 59.3%

融点: 170°C (dec.)

Anal. Calcd.: C 38.22; H 5.70; N 4.95

Found: C 37.99; H 5.61; N 4.79

IR ν KBr/max cm^{-1} : 1735, 1660 (C=O), 860 (Ge-O)

$^1\text{H-NMR}$ (D_2O) δ : 1.22, 1.25 ($3\text{H}\times 2$, s $\times 2$, $\text{Ge-C-}(\text{CH}_3)_2$), 1.30 (3H, t, $\text{CH}_2\text{-CH}_3$), 2.11 (3H, s, CO-C-CH_3), 4.27 (2H, br, CH_2), 4.80 (1H, s, CO-CH)

【0045】1-(1-アセトアミド-1-エトキシカルボニルメチル)-1-メチルプロピルゲルマニウムセスキオキサイド(式(3)において、 $\text{R}_1=\text{R}_4=\text{CH}_3$, $\text{R}_2=\text{CH}_2\text{CH}_3$ の化合物)

収率: 32.2% (ジステレオマーの混合物)

融点: 175°C (dec.)

Anal. Calcd.: C 40.46; H 6.11; N 4.72

Found: C 40.21; H 5.92; N 4.55

IR ν KBr/max cm^{-1} : 1730, 1660 (C=O), 860 (Ge-O)

$^1\text{H-NMR}$ (CH_3OD): 1.08 ($3\text{H}\times 2$, br, Ge-C-C-CH_3), 1.28 ($6\text{H}\times 2$, br, Ge-C-CH_3 , O-C-CH_3), 1.73 ($2\text{H}\times 2$, br, Ge-C-CH_2), 2.04 ($3\text{H}\times 2$, br, CO-CH_3), 4.19 ($2\text{H}\times 2$, br, O-CH_2), 4.86 (1H $\times 2$, br, CO-CH)

【0046】

【表3】

R_1	R_2	R_3	R_4	収率
CH_2CH_3	H	CH_2CH_3	CH_3	57.0
$\text{CH}_2\text{CH}_2\text{CH}_3$	H	CH_2CH_3	CH_3	61.3
H	CH_2COOH	CH_2CH_3	CH_3	58.2
H	$\text{p-OH-C}_6\text{H}_5$	CH_2CH_3	CH_3	60.9

【0047】実施例4

式(3)で表される本発明化合物(但し $\text{R}_3=\text{H}$)の合成

a) 2-アセトアミド-3-ゲルミルブタン酸(式

(1)において、 $\text{Y}=\text{H}$, $\text{R}_1=\text{H}$, $\text{R}_2=\text{R}_4=\text{CH}_3$ の化合物)をメタノールとジクロルメタンとの混合溶媒に溶解し、メタクロル過安息香酸3.94gを加え、室温

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で30分間攪拌した。反応終了後、析出した沈殿を濾取し、エーテルで洗浄することにより、1-(1-アセトアミド-1-カルボキシメチル)エチルゲルマニウムセスキオキサイド(式(3)において、 $\text{R}_1=\text{H}$, $\text{R}_2=\text{R}_4=\text{CH}_3$ の化合物)を無色の粉末として1.0g得た。

収率: 60.1% (ジステレオマーの混合物)

融点: 257°C (dec.)

Anal. Calcd.: C 38.22; H 5.70; N 4.95

Found: C 38.13; H 5.52; N 4.01

IR ν KBr/max cm^{-1} : 3700~2900 (NH, OH), 1720, 1650 (C=O), 880, 820 (Ge-O)

$^1\text{H-NMR}$ (D_2O) δ :

ジステレオマー a 1.15 (3H, d, CH_3), 2.07 (3H, s, $\text{CH}_3\text{-CO}$), 2.26 (1H, dq, Ge-CH), 4.82 (1H, d, N-C-H)

ジステレオマー b 1.26 (3H, d, CH_3), 2.06 (3H, s, $\text{CH}_3\text{-CO}$), 2.22 (1H, dq, Ge-CH), 4.44 (1H, d, N-C-H)

【0048】b) 2-アセトアミド-3-(パラアセトキシフェニル)-3-トリクロルゲルミルプロパン酸(式(1)において、 $\text{Y}=\text{Cl}$, $\text{R}_1=\text{H}$, $\text{R}_2=\text{パラアセトキシフェニル}$, $\text{R}_3=\text{H}$, $\text{R}_4=\text{CH}_3$ の化合物)

1.88gを水に溶解し、炭酸水素ナトリウム1.78gを加え、室温で20時間攪拌した後、1Nの水酸化ナトリウム水溶液4.4mlを加え、更に2時間攪拌した。反応終了後、希塩酸を加えてpH7とし、メタノールを加えて濾過した。濾過液を濃縮し、残渣にメタノールを加え、析出した沈殿を濾取する操作を2回行い、

0.82gの黄色粉末を得た。これを蒸留水に溶解し、陽イオン交換樹脂アンバーライトIR120B(商品名)【H+型】と一晚攪拌後、水層を濃縮することにより、2-アセトアミド-2-カルボキシ-1-パラヒドロキシフェニルエチルゲルマニウムセスキオキサイド(式(3)において、 $\text{R}_1=\text{H}$, $\text{R}_2=\text{パラヒドロキシフェニル}$, $\text{R}_4=\text{CH}_3$ の化合物)を微黄色の粉末として700mg得た。

収率: 58.9% (ジステレオマーの混合物)

融点: 300°C <(dec.)

Anal. Calcd.: C 38.22; H 5.70; N 4.95

Found: C 38.00; H 5.51; N 4.72

IR ν KBr/max cm^{-1} : 3600~2500 (NH, OH), 1710, 1640 (C=O), 875, 840 (Ge-O)

$^1\text{H-NMR}$ (D_2O) δ : 1.87 (3H, s, $\text{CH}_3\text{-CO}$), 3.55 (1H, d, Ge-CH), 4.98 (1H, d, N-CH), 6.87 (2H, d, OHのオルト位), 7.04 (2H, d, OHのメタ位)

【0049】c) 1-(1-アセトアミド-1-エトキシカルボニルメチル)-2-メチルプロピルゲルマニウムセスキオキサイド(式(3)において、 $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}(\text{CH}_3)_2$, $\text{R}_3=\text{CH}_3\text{CH}_2$, $\text{R}_4=\text{CH}_3$ の化合物)2.97g(0.005mol)を80mlの水

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に懸濁し、水酸化ナトリウム0.44g (0.011mol)を加えて17時間攪拌した。反応終了後、濾過し、濾液を陽イオン交換樹脂アンバーライトIR120B (商品名) [H+型]に通して脱ナトリウムした後、濾液を濃縮乾固することにより、1-(1-アセトアミド-1-カルボキシメチル)-2-メチルプロピルゲルマニウムセスキオキサイド (式(3)において、 $R_1=H$, $R_2=CH(CH_3)_2$, $R_4=CH_3$ の化合物)を微黄色の粉末として1.36g得た。

収率: 50.6%

融点: 207°C(dec.) Anal. Calcd.: C35.75; H5.25; N5.21

Found: C35.56; H5.06; N5.20

IR ν KBr/max cm^{-1} : 1740, 1665 (C=O), 875 (Ge-O)

1H -NMR ($D_2O+NaOD$) δ : 1.06, 1.08 (6H, d, $(CH_3)_2$), 2.06 (3H, s, CO-CH₃), 1.83~2.33 (2H, m, CH-CH), 4.56 (1H, d, CO-CH)

【0050】d) 尚、式(3)で表される他の化合物も、上記a、b又はcに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表4に例示するとおりである。

【0051】2-アセトアミド-2-カルボキシ-1,1-ジメチルエチルゲルマニウムセスキオキサイド (式(3)において、 $R_1=R_2=CH_3$, $R_4=CH_3$ の化合物)

収率: 82.5%

融点: 210°C(dec.)

Anal. Calcd.: C33.00; H 4.75; N5.50

Found: C32.71; H 4.61; N 5.27

IR ν KBr/max cm^{-1} : 1720, 1650 (C=O), 880 (Ge-O)

1H -NMR (D_2O) δ : 1.08 (3H, s, CH_3), 1.17 (3H, s, *

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* CH_3), 2.11 (3H, s, CO-CH₃), 4.62 (1H, s, CO-CH)

^{13}C -NMR (D_2O , NaOD) δ : 22.64, 23.71 ($(CH_3)_2$), 24.98 (CO-CH₃), 38.54 (Ge-C), 64.28 (CH), 176.68, 180.06 (COO, CON changeable)

【0052】1-(1-アセトアミド-1-カルボキシメチル)-1-メチルプロピルゲルマニウムセスキオキサイド (式(3)において、 $R_1=CH_3$, $R_2=CH_2CH_3$, $R_4=CH_3$ の化合物)

収率: 71.7% (ジアステレオマーの混合物)

10 融点: 184°C(dec.)

Anal. Calcd.: C35.75; H5.25; N5.21

Found: C35.63; H5.19; N 5.19

IR ν KBr/max cm^{-1} : 1720, 1660 (C=O), 870 (Ge-O)

1H -NMR ($D_2O+NaOD$) δ : ジアステレオマー a 1.01 (3H, t, CH_3), 1.36 (1H, dq, CH_3-CH_2), 1.67 (1H, dq, CH_2-CH), 1.09 (3H, s, Ge-C- CH_3), 2.10 (3H, s, CO- CH_3), 4.82 (1H, s, CO-CH)

ジアステレオマー b 0.99 (3H, t, CH_3), 1.50 (2H, dq, CH_3-CH_2), 1.15 (3H, s, Ge-C- CH_3), 2.10 (3H, s, CO- CH_3), 4.65 (1H, s, CO-CH)

^{13}C -NMR (D_2O , NaOD) δ : ジアステレオマー a 13.24 (Ge-C- CH_3), 20.73 (CH_3), 24.78 (CO- CH_3), 30.77 (CH₂), 46.90 (Ge-C), 58.61 (CH-CO)

ジアステレオマー b 12.96 (Ge-C- CH_3), 21.36 (CH_3), 24.83 (CO- CH_3), 27.94 (CH₂), 47.33 (Ge-C), 62.41 (CH-CO)

a, b 177.10, 177.13, 180.19, 180.67 (COO, CON changeable)

【0053】

【表4】

R_1	R_2	R_3	R_4	収率
CH_2CH_3	H	H	CH_3	96.9
$CH_2CH_2CH_3$	H	H	CH_3	78.2
H	CH_2COOH	H	CH_3	83.1

【0054】実施例5

式(4)で表される本発明化合物 (但し $R_3=H$) の合成

a) 2-アミノ-3-(トリクロロゲルミル)-ペンタン酸塩 (式(2)において、 $X=Y=Cl$, $R_1=H$, $R_2=CH_2CH_3$ の化合物) 8.29g (0.025mol) を100mlの水に溶解し、陽イオン交換樹脂アンバーライトIR120B (商品名) [H+型]に吸着させて水洗した後に2Nのアンモニア水で溶出し、濾液を乾固することにより、1-(1-アミノ-1-カルボキシメチル)-プロピルゲルマニウムセスキオキサイド (式(4)において、 $R_1=H$, $R_2=CH_2CH_3$ の※50

※化合物)を微黄色の粉末として4.62g得た。

40 収率: 86.9%

融点: 206°C(dec.)

Anal. Calcd.: C 28.23; H 4.74; N 6.5

Found: C 28.06; H 4.59; N 6.44

IR ν KBr/max cm^{-1} : 1630 (C=O), 870 (Ge-O)

1H -NMR (D_2O) δ : 1.09 (3H, t, CH_3), 1.51 (1H, dd, CH_3-CH_2), 1.74 (1H, dd, CH_2-CH), 2.09 (1H, dd, Ge-CH), 4.19 (1H, d, CO-CH)

^{13}C -NMR (D_2O) δ : 15.67 (CH_3), 19.82 (CH_3-CH_2), 40.51 (Ge-CH), 57.70 (CH-N), 176.20 (CO)

【0055】b) 2-アセトアミド-3-(パラアセト

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キシフェニル) - 3-トリクロルゲルミルプロパン酸
(式(1)において、 $Y=Cl$ 、 $R_1=H$ 、 $R_2=パラ$
セトキシフェニル、 $R_4=CH_3$ の化合物) 969mgに
濃塩酸を加え、室温で2日間攪拌した。反応終了後、内
容物を多量の水中に注ぎ不純物を濾過した。濾液を濃縮
して得た残渣を蒸留水に溶解し、陽イオン交換樹脂アン
バーライトIR120B (商品名) [H+型] に吸着さ
せ、5%アンモニア水で溶出し、溶出液を濃縮すること
により、2-アミノ-2-カルボキシ-1-パラハイド
ロキシフェニルエチルゲルマニウムセスキオキサイド
(式(4)において、 $R_1=H$ 、 $R_2=パラハイドロキシ$
フェニルの化合物) を微黄色の粉末として200mg得
た。

収率: 46.2% (ジアステレオマーの混合物)

融点: 300°C(dec.)

Anal. Calcd.: C 28.23; H 4.74; N 6.5

Found : C 28.00; H 4.56; N 6.32

IR ν KBr/max cm^{-1} : 3700~2200 (NH $^{+}$), 1630 (NH $^{+}$), 1605 (C=O), 885, 845 (Ge-O)

1H -NMR (D $_2$ O) δ : 3.38 (1H, d, Ge-CH), 4.33 (1H, d, CO-CH), 6.87 (2H, d, OHのオルト位), 7.14 (2H, d, OHのメタ位)

【0056】 c) 1-(1-アセトアミド-1-カルボキシメチル) エチルゲルマニウムセスキオキサイド (式(3)において、 $R_1=H$ 、 $R_2=CH_3$ 、 $R_4=CH_3$ の化合物) 200mgを水に溶解し、更に濃塩酸0.2mlを加え、18時間加熱還流した。反応終了後、反応液を濃縮し、得られた白色結晶を水に再度溶解して不純物を濾過し、濾液を陽イオン交換樹脂アンバーライトIR120B (商品名) [H+型] に通した。十分に水洗をした後、5.6%アンモニア水で溶出し、溶出液を濃縮することにより、1-(1-アミノ-1-カルボキシメチル) エチルゲルマニウムセスキオキサイド (式(4)において、 $R_1=H$ 、 $R_2=CH_3$ の化合物) をオフホワイトの粉末として126mg得た。

収率: 76.3%

融点: 270°C(dec.)

Anal. Calcd.: C 24.18; H 4.06; N 7.05

Found : C 24.00; H 3.88; N 6.91

IR ν KBr/max cm^{-1} : 3800~2500 (NH, OH), 1610 (C=O), 840, 790 (Ge-O)

1H -NMR (D $_2$ O) δ :

ジアステレオマー a 1.19 (3H, t, CH $_3$), 2.19 (1H, dq, Ge-CH), 4.19 (1H d, CO-CH)

ジアステレオマー b 1.36 (3H, t, CH $_3$), 2.09 (1H, dq, Ge-CH), 3.86 (1H d, CO-CH)

【0057】 d) 尚、式(4)で表される他の化合物も、上記 a、b 又は c に記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表5に例示するとおりである。

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【0058】 1-(1-アミノ-1-カルボキシメチル) - 2-メチルプロピルゲルマニウムセスキオキサイド (式(4)において、 $R_1=H$ 、 $R_2=CH(CH_3)_2$ の化合物)

収率: 71.0%

融点: 191°C(dec.)

Anal. Calcd.: C 31.78; H 5.33; N 6.18

Found : C 31.48; H 5.09; N 6.10

IR ν KBr/max cm^{-1} : 1630 (C=O), 860 (Ge-O)

1H -NMR (D $_2$ O) δ : 1.01, 1.15 (6H, d, (CH $_3$) $_2$), 2.17 (1H, d sept, (CH $_3$) $_2$ -CH), 2.29 (1H, dd, Ge-CH), 4.18 (1H, d, CH-CO)

^{13}C -NMR (D $_2$ O) δ : 22.71, 25.84 ((CH $_3$) $_2$), 27.80 ((CH $_3$) $_2$ -CH), 46.03 (Ge-CH), 56.89 (CH-N), 177.13 (C=O)

【0059】 1-(1-アミノ-1-カルボキシメチル) - 1-メチル-エチルゲルマニウムセスキオキサイド (式(4)において、 $R_1=R_2=CH_3$ の化合物)

収率: 80.0%

融点: 190°C(dec.)

Anal. Calcd.: C 28.23; H 4.74; N 6.58

Found : C 28.04; H 4.64; N 6.56

IR ν KBr/max cm^{-1} : 1640 (C=O), 850 (Ge-O)

1H -NMR (D $_2$ O) δ : 1.53 (3H, s, CH $_3$), 1.36 (3H, s, CH $_3$), 3.95 (1H, s, CH)

【0060】 1-(1-アミノ-1-カルボキシメチル) - 1-メチル-プロピルゲルマニウムセスキオキサイド (式(4)において、 $R_1=CH_3$ 、 $R_2=CH_2CH_3$ の化合物)

収率: 84.6% (ジアステレオマーの混合物)

融点: 195°C(dec.)

Anal. Calcd.: C 31.78; H 5.33; N 6.18

Found : C 31.53; H 5.44; N 6.11

IR ν KBr/max cm^{-1} : 1650 (C=O), 845 (Ge-O)

1H -NMR (D $_2$ O) δ : 1.06 (3H \times 2, t, Ge-C-C-CH $_3$), 1.17, 1.38 (3H \times 2, s \times 2, Ge-C-CH $_3$), 1.30~2.27 (2H \times 2, m, Ge-C-CH $_2$), 4.00, 4.19 (1H \times 2, s \times 2, CO-CH)

【0061】 2-アミノ-2-カルボキシ-1-(カルボキシメチル) エチルゲルマニウムセスキオキサイド

(式(4)において、 $R_1=H$ 、 $R_2=CH_2COOH$ の化合物)

収率: 74.21% (ジアステレオマーの混合物)

融点: 345°C(dec.)

IR ν KBr/max cm^{-1} : 1663 (C=O)

1H -NMR (D $_2$ O) δ : 2.33~2.85 (3H, Ge-CH-CH $_3$), 4.10 (1H, CH-N)

^{13}C -NMR (D $_2$ O, dioxane) δ : 31.22, 31.44 (Ge-CH $_2$ -CH $_2$), 34.29, 34.56 (Ge-CH), 52.16, 57.19 (CH-N), 174.2, 179.7 (C=O)

50 【0062】

[表5]

R_1	R_2	R_3	収率
CH_2CH_3	H	H	86.9
$\text{CH}_2\text{CH}_2\text{CH}_3$	H	H	80.5
H	CH_3	CH_2CH_3	81.3
CH_3	CH_3	CH_2CH_3	84.2

[0063]

【参考実験】本発明化合物によるメイラード反応の阻害効果

1. 試料溶液の調製

原液

$\text{N}\alpha\text{-t-Boc-L-Lysine}$ (50mM)、グルコース (1M) を 50ml の磷酸緩衝液 240ml に溶解して原液とした。

コントロール液

原液 30ml に 50ml の磷酸緩衝液 30ml に溶解してコントロール液とした。

10 * 有機ゲルマニウム化合物液

有機ゲルマニウム化合物のそれぞれ 20mM をとり、50mM の磷酸緩衝液に溶解して 50ml とし、そのうちの 30ml を原液 30ml と混合し、10mM の有機ゲルマニウム化合物液とした。

【0064】2. 阻害効果の試験及び結果

上記各試料溶液を混合し、40℃の振盪条件下でインキュベートし、4、8、11 日目それぞれから試料を採取し、297nm (極大吸収) における吸光度を測定した。

結果を以下の表6に示す。

* 20 [表6]

化合物			吸光度(297nm)		
R_1	R_2	R_3	4日目	8日目	11日目
H	CH_2CH_3	H	0.37	0.54	1.35
H	$\text{p-OH-C}_6\text{H}_5$	H	0.34	0.53	1.31
H	CH_3	H	0.39	0.55	1.26
H	$\text{CH}(\text{CH}_3)_2$	H	0.33	0.55	1.30
CH_3	CH_3	H	0.33	0.51	1.25
CH_3	CH_2CH_3	H	0.32	0.52	1.21
H	CH_2COOH	H	0.31	0.55	1.19
CH_2CH_3	H	H	0.33	0.53	1.15
H	CH_3	CH_2CH_3	0.30	0.47	1.08
CH_3	CH_3	CH_2CH_3	0.29	0.48	1.05
H	H	H	0.39	1.17	2.78
C_6H_5	H	H	0.41	1.26	2.55
コントロール			0.50	1.51	3.13